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Antithrombotic treatment and major adverse cardiac events after bleeding in patients with myocardial infarction: a retrospective analysis of nationwide registry data

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Abstract

Aims: The aim of this study was to describe the use of antithrombotic therapy following a bleeding event among patients with myocardial infarction (MI), and the associated risk of major adverse cardiac events (MACE).

Methods and Results: Using Danish nationwide registries patients hospitalized with a bleeding event within 1 year after MI were identified. Antithrombotic treatment with aspirin, clopidogrel and/or vitamin K antagonists (VKA) was determined at the bleeding and at Day 90 and 180 post bleed. Based on guidelines, patients were stratified into four groups: expected, reduced, discontinued, or intensified treatment. Risk of MACE (ischemic stroke, MI, or death) within the first year was assessed by Cox proportional hazard models. A total of 3324 patients with a bleeding after MI were included. At day 90 post bleed 1052 (31.7%) received expected antitrombotic treatment, 1301 (39.2%) reduced, 164 (4.9%) intensified, and 807 (24.3%) no treatment. MACE occurred in 637 (19.2%) patients. With dual antiplatelet therapy (DAPT) as reference, adjusted hazard ratios for MACE were: aspirin 1.81 (1.06-3.09), clopidogrel 1.08 (0.64-1.82), VKA 1.08 (0.47-2.48), VKA+aspirin 1.97 (0.95- 4.07), VKA+clopidogrel 0.26 (0.03-1.91), triple 1.73 (0.50-5.95), no treatment 1.93 (1.11-3.36).

Conclusions: The majority of MI patients reduced or discontinued their antithrombotic therapy post-bleed. Patients in monotherapy with aspirin or no treatment post-bleed had a higher risk of MACE Further studies of optimal antithrombotic treatments after a bleed are needed.

Keywords: Myocardial infarction, bleeding, antithrombotic treatment

Introduction:

Antithrombotic therapy is a cornerstone of treatment in patients with acute myocardial infarction (MI).[1, 2] Along with an early invasive strategy of coronary angiography and revascularization, antiplatelet treatments have reduced the incidence of recurrent thrombotic events and death.[3] However, many MI patients have additional indications for oral anticoagulation (OAC), i.e. atrial fibrillation or mechanical prosthetic heart valves,[3, 4] and combinations of antithrombotic drugs are widely used.[5, 6] In addition to the desired antithrombotic effect, antithrombotic pharmacotherapy is associated with an increased risk of bleeding, this risk is accentuated with the number of drugs used, and with certain combinations.[5] Several randomized trials have shown 30 days-risk of major bleeding of 1-8% among MI patients, whereas observational studies suggest an even higher bleeding rate up to 12%. [7-9]

It is well established that patients who experience a bleeding have a higher risk of recurrent thrombotic events and death following the bleed.[10-13] Discontinuation of antithrombotic drugs leading to progressive recovery of platelet function and coagulation activity has been put forward as one of the underlying mechanisms. However, the clinical use of antithrombotic treatment in MI patients after a bleeding event is sparsely described. In addition, it is unknown, whether there is an association between antithrombotic treatment strategy post-bleed and the risk of recurrent thrombotic events and death.

The purpose of this study was to describe antithrombotic treatment therapy after a bleeding event among MI patients and in addition to assess the associated risk of major adverse cardiac events (MACE).

Methods:

Data sources:

This study was conducted by use of four nationwide registries, which were linked on an individual level by a unique personal identification number: 1) Danish National Patient Registry: contains information about all hospital admissions since 1978 and the associated discharge diagnoses according to the International

Classification of Diseases (ICD-8 and ICD-10) 2) The Danish Registry of Medicinal Product Statistics (The National Prescription Register): holds information about all claimed prescriptions since 1995. This includes information about date of dispensing, total quantity, strength and the international anatomical therapeutic chemical classification system (ATC) code. 3) The Danish Civil Registry: holds information on vital status, residency, migration and ancestry of each Danish citizen 4) The Danish Registry of Causes of Death: contains information on death since 1970.

Ethics:

Registry studies in which individuals cannot be identified do not require ethical approval in Denmark. This study was approved by the Danish Data Protection Agency (No. 2007-58-0015; internal reference: GEH 2014-014, I-Suite no. 02732).

Study population:

By use of the Danish National Patient Registry, we identified patients aged 30 years or above who were hospitalized with first time MI (ICD-10 code I21 or I22) between the years 2000 and 2012. We included those admitted with a bleeding event within the first year post-MI. Inclusion date was the day of hospital admission due to bleeding. A bleeding admission was defined as admission to hospital with a bleeding diagnosis (ICD-10 codes for bleeding diagnoses listed in appendix I). [14, 15] The period of one year was chosen as patients during this period are recommended intensified antithrombotic treatment. Patients, who were in no antithrombotic treatment at the bleeding event were excluded. No treatment was defined as no claimed prescriptions/no tablets available from previous claimed prescriptions. Furthermore patients, who died within 90 days post-bleed, were excluded to avoid immortal lifetime bias. [16] Flow chart is shown as Figure 1.

Comorbidity and pharmacotherapy: Hospitalizations within the year prior to the bleeding were used to define comorbidities according to the Modified Ontario acute myocardial infarction mortality prediction rules.[17] Because of low sensitivity of heart failure diagnoses, claimed prescriptions of loop diuretics within 90 days before admission as a proxy for heart failure.[18] Patients with claimed prescriptions for glucose-lowering agents were considered to have diabetes. Patients were classified by percutaneous coronary intervention (PCI), using the Danish procedure codes KFNG02 and KFNG05. Baseline pharmacotherapy (ACE-inhibitors, beta-blockers, antidiabetics, PPI, NSAIDs, loop diuretics, spironolactone and statins) was assessed, if a prescription was dispensed within 180 days prior to the bleeding event. Likewise, prescriptions of antithrombotics were used to assess antithrombotic treatment regimen.[5, 19] Because the inclusion period was from 2000-2012 only 5.4% of the MI patients received prasugrel/ticagrelor or NOAC after the MI and we chose to exclude these patients to uniform the population.

Endpoints:

The following endpoints were defined:

1) **Antithrombotic** treatment at the following time points: at baseline, first claimed antithrombotic regimen within 90 days post-bleed, at day 90 and day 180 post-bleed.

2) **Claimed antithrombotic treatment versus expected treatment:**

   Patients were classified in the following groups: expected treatment, reduced treatment, no treatment or intensified treatment. The ongoing antithrombotic treatment was evaluated at baseline, at the first claimed regimen post-bleed, at day 90 and day 180 post-bleed.

   The following criteria were used to define expected regimens:

   - *Antiplatelet therapy:* According to Guidelines 12 months treatment with dual antiplatelet therapy (DAPT) was expected after the MI diagnose. After 12 months, patients were

expected to be in lifelong monotherapy with aspirin or clopidogrel, unless they had an indication of OAC.[3, 20, 21] If the patient had an elective PCI within the first year post-MI, the DAPT period was extended 6 months after the date of PCI.[22]

- *Oral anticoagulation:* Lifelong therapy of OAC was expected in patients with a diagnosis of mechanical heart valve, recurrent Pulmonary Embolism/Deep Venous Thrombosis (≥ 1 event) and/or atrial fibrillation (AF) and CHA2DS2-VASc-score ≥ 1 at inclusion. In patients with first time pulmonary embolism or deep venous thrombosis, 6 months of OAC was expected. (diagnose codes and definition of CHA2DS2-VASc in Appendix I)
- *Combinations of antiplatelets and oral anticoagulation:* OAC and DAPT was expected for 1 year after the MI, if the indication of OAC was present at the MI diagnosis. If the indication of oral coagulation arose after the MI, or if it was temporary (first time PE/deep venous thrombosis) the expected period was adjusted accordingly.

The following criteria were used to define reduced treatment: The patient was classified to have reduced treatment if he/she claimed less antithrombotic medication than expected (Supplementary Figure 2) and intensified treatment: The patient was classified to have intensified treatment if he/she claimed more antithrombotic medication than expected (Supplementary Figure 2).

3) Associated risk of major adverse cardiac events (MACE):

The associated risks of MACE were defined as recurrent MI, ischemic stroke or all-cause death, within the first year post-bleed, calculated from day 90 post-bleed. Definitions listed in the appendix.[23] Patients were censored at first event.

Additional analyses:

A sub-analysis of recurrent bleeding events was carried out, starting from day 90 post-bleed. A recurrent bleeding event was defined using the same ICD-10 discharge codes as at baseline (Appendix I). Patients were censored at first event.

Furthermore, a sub-analysis of the patients with or without OAC at baseline and related outcomes were assessed.

Statistical analyses:

Categorical variables are presented in number and percentages, and continuous variables are presented with a mean/standard deviation or median/interquartile ranges. The antithrombotic treatments post bleed were assessed as first regimen within 90 days post-bleed, at Day 90 and Day 180 post-bleed. Sensitivity analyses on shorter intervals were tested (antithrombotic treatment at day 30 and day 60), but due to largely varying prescription lengths, we chose 90 days as the period. To assess the risk of MACE we used two different Cox Proportional Hazard Models. One included the antithrombotic drug exposure groups as time-varying covariates. Days where the patients were admitted was covered by medicine supplied by the hospital. With this model, patients were only considered at risk for each exposure group while taking the corresponding antithrombotic drug or were without treatment. Each patient was allowed in one drug exposure group at a time; however it was possible to change exposure group based on claimed prescriptions, as done previously. [5, 19] The analyses were adjusted for relevant covariates as age groups, sex, comorbidity, concomitant medical therapy and PCI status. Due to non-linear distribution, age was included as age groups of <60 years, 60-70 years, 70-80 years and >80 years. The second model included information of antithrombotic treatment after the bleeding categorized in following categories: no change, discontinued, reduced or intensified treatment. This model was adjusted for age groups, sex, comorbidity, concomitant medical therapy and PCI status. The models were tested for absence of relevant interactions and found to be valid. Results are presented as hazard ratios (HR) with 95% Confidence Intervals (CI).

All statistical analyses were done using SAS version 9.4 (SAS institute Inc., Cary, NC, USA).

Results:

This study included 3324 patients with first-time myocardial infarction (MI), who were admitted with a bleeding event within one-year post-MI (Figure 1). Table 1 shows the baseline characteristics. Mean age was 71.2 (SD 11.5) for men and 75.4 (SD 11.4) for women.

Antithrombotic treatment post-bleed:

Mean time from bleeding to claimed prescription of antithrombotic treatment varied from 24.2 days (SD 25.3) for triple therapy to 42.2 days (SD 26.8) for monotherapy with aspirin (Table 2). The majority of patients (78.8%) were in monotherapy with aspirin or clopidogrel or in no treatment within the first 90 days post bleed. Treatment patterns at day 90 and day 180 post-bleed are shown in Table 2. At day 180 post bleed, the largest group was in monotherapy with aspirin (33.0%) followed by DAPT (24.2%). Table 3 shows the proportion of patients in expected, reduced, intensified or no treatment. A discontinuation or reduction was observed in >70% of the patients after the bleeding event. Baseline characteristics according to expected treatment are presented in the appendix, supplementary Table 1a, 1b and 1c. Comparing patients with or without OAC: Patients without OAC were more likely to be in expected treatment (at all time points), more discontinued treatment at first regimen and Days 90, whereas patients with OAC at all time points were more likely to received reduced or intensified treatment. Numbers are shown in Supplemental Table 3.

Major adverse cardiac events (MACE):

A total of 637 (19.2%) patients experienced MACE: 149 (4.5%) had a recurrent myocardial infarction, 73 (2.1%) had a stroke and 415 (12.5%) died. Results from the Cox analyses are shown in Figure 2a+2b. Compared with DAPT, no antithrombotic treatment and monotherapy with aspirin were associated with an increased risk of major adverse cardiac events, the remaining antithrombotic exposure groups were not

significantly associated with an increased or decreased one-year risk of MACE. Other variables associated with increased risk of MACE were: increasing age, renal failure, heart failure, malignancy and use of proton pump inhibitors. In relation to expected treatment discontinuation was at all timepoints associated with increased risk of MACE. At Day 90 intensified treatment was also associated with increased risk of MACE, but not at first regimen or at Day 180. In the subgroup analysis of patients with OAC no treatment at Day 90 was associated with a higher risk of MACE, as was both no and reduced treatment at Day 180.

Recurrent bleeding events:

A total of 431 (12.9%) patients had a recurrent bleeding event within one year. The distribution was following: urogenital bleeding event in 115 patients (3.5%), GI bleeding 108 patients (3.2%), anemia of acute or chronic bleeding 95 patients (2.8%), respiratory tract bleedings 88 patients (2.6%) and cerebral bleeding in 25 patients (0.8%). The Cox analyses did not show any significant associations between antithrombotic treatment regimen post-bleed and risk of recurrent bleeding events (supplementary appendix Table 1), expect in the subgroup of patients with OAC, where no treatment at first regimen and Day 90 was associated with a lower risk of bleeding.

Discussion:

This study is one of the first to describe the pattern of antithrombotic treatment after a bleeding event among patients with recent MI and the associated risk of major adverse cardiac events. The main findings are: 1. The majority of patients (79.7%) either discontinued or were reduced in their antithrombotic treatment within the first 90 days after the bleed. At day 90 and day 180 post-bleed, this number had declined, however more than 50% of the patients were still in no or reduced antithrombotic treatment. 2. We found that the risk of major adverse cardiac events (MACE) was significantly increased among patients, who were in no antithrombotic treatment or monotherapy with aspirin post-bleed. 3. We found no associations between the antithrombotic treatment post-bleed and risk of recurrent bleeding events.

Bleeding is a frequent complication among patients with acute coronary syndrome; up to 30% experience bleeding events of varying severity during the hospitalization.[11, 24, 25] Patients who bleed are in our and in other studies older and have more co-morbidities, including a history of prior stroke, heart failure, diabetes mellitus and PCI prior to the event. [8, 9] Previous studies have investigated the prognostic impact of bleeding episodes among patients with acute coronary syndrome, and have reported, that a major bleeding event was associated with a 5-fold increase in risk of death during the first 30 days. [10] The association was weaker between 30 days and 6 months, however mortality was still increased, and a similar pattern was seen for recurrent ischemic events (MI and stroke).[10] Another study by Rao et al. showed a stepwise increase in 30-day and 6 month mortality associated with increasing bleeding severity.[11] These findings have been supported by others.[8, 26, 27] Thus major bleeding is associated with a higher short- and long term mortality, and even minimal bleeding is of clinical significance.[26, 28]

Lopes and colleagues reported a lower likelihood of receiving clopidogrel at discharge after an in-hospital bleeding among ACS patients treated with a PCI, whereas there was no significant difference in the use of aspirin.[9] In a study by Chan et al., discharge antithrombotic use was examined among 8582 ACS patients with in-hospital bleeding.[29] Almost 1 of 10 patients with bleeding was discharged without antiplatelets, and these patients had a higher risk of death, MI and stroke at six months, compared with patients receiving antiplatelets at discharge. This supports our findings, that absence of antithrombotic therapy post-bleed may contribute to the increased risk of ischemic events.[29] Wang et al. found differences in antiplatelet use after bleeding during index AMI hospitalization, a difference that persisted up to 6 months, but disappeared after one year.[30] Our results also indicate, that some patients resume their antithrombotic treatment within 6 months post-bleed.

The Patterns of non-adherence to Antiplatelet Regimens in stented Patients (PARIS)-study investigated DAPT cessation among patients undergoing PCI. They found that approximately 3% had ceased DAPT within 30 days and 20% within the first year after PCI. [31]The majority disrupted DAPT due to non-compliance or bleeding. Physician recommended cessation was associated with a lower risk of MACE, while no difference

was found among the group of temporary interruption due to surgical procedure. A disruption due to bleeding or non-compliance was associated with a higher risk of MACE.[31]

Clearly, it is a clinical challenge to assess the risk and benefit of antithrombotic treatment after a bleeding event. Several studies have published recommendations on the acute management of bleeding; however less is known about the management of antithrombotic treatment after the bleeding event among MI patients. The European Society of Cardiology recently published a consensus paper, where it is recommended to consider resumption of antithrombotic drugs in patients with a clear indication, except if the bleeding is life-threatening.[32] Our findings support this approach as we found increased risk of MACE among patients receiving no treatment/or aspirin monotherapy post-bleed. Our study demonstrates that it is most common to reduce/or discontinue treatment after the bleeding event, and resume treatment after a period of time, a practice that is supported by the same consensus document.

The patients that discontinued or reduced treatment were older, with more comorbidity as congestive heart failure, cerebrovascular disease, renal failure and atrial fibrillation compared with the patients in expected treatment. In addition, a lower number had been treated with PCI. Patients treated with OAC were likewise older with more comorbidity compared with those in dual antiplatelet therapy and were more likely to received reduced or intensified treatment at all time-point. This probably indicates a clinical dilemma where patients have both high risk of bleeding and thrombotic events. At Day 90 we found that intensified treatment was also associated with increased risk of MACE, but not at other time points. The findings are in a small patient group and might be explained by patients initiating OAC due to atrial fibrillation and concurrent increased risk stroke.(4)

Strengths and limitations:

The main strength of our study is the completeness of data with a large nationwide unselected cohort of MI patients with complete information of prescriptions. However, our study has several limitations. We only included MI patients who were admitted for a bleeding and survived > 90 days, thus our population

represents a small proportion of an all-comer MI population and minor bleedings are not considered. Our data do not comprise reasons for prescription or cessation of medication, which is important in evaluation of the risk/benefit among different patient groups. Also, the accuracy of the antithrombotic regimens post-bleed is dependent on a prescription claim, and indirectly on the number of tablets from the previous prescription. If patients had claimed a large number of tablets before the bleeding, they would have a longer period until the next prescription but might have initiated treatment sooner, with tablets available from the previous purchase. We have implemented a 90-days period after bleeding to minimize this problem. The observational study design increases the risk of residual confounding, even after adjustment. At last, MACE was defined as admittance to a Danish hospital with recurrent MI, stroke or death. Those patients not admitted with MI or stroke/or admitted outside Denmark could not be classified, however the problem is considered minor, and data on vital status was complete in all patients.

In conclusion, among patients with a bleeding post-MI, the majority reduced or discontinued antithrombotic therapy post-bleed. A higher risk of MACE was related to discontinuation of antithrombotic therapy or reduction to monotherapy with aspirin. Further studies of optimal antithrombotic treatments after a bleeding event are needed.

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Figure Legends:

Figure 1: Flowchart of patient selection

Figure 2a+2b: Adjusted one-year risk of MACE in MI patients with a bleeding event Risk of within the first year post bleed.

Table

Table 1. Baseline, according to anti-thrombotic treatment at bleeding event.

		Monotherapy			Dual therapy			Triple therapy
	All patients (n=3324)	**Aspirin** (n=888)	**Clopidogrel** (n=332)	**VKA** (n=62)	**Aspirin+ Clopidogrel** (n=1536)	**Aspirin+VKA** (n=354)	**Clopidogrel+VKA** (n=67)	**Aspirin+ Clopidogrel+VKA** (n=85)
Inclusion Year								
2000-2003	871 (26%)	453 (51%)	58 (18%)	22 (35%)	205 (13%)	120 (34%)	8 (12%)	5 (6%)
2004-2006	970 (29%)	201 (23%)	113 (34%)	9 (15%)	503 (33%)	99 (28%)	22 (33%)	23 (27%)
2007-2009	899 (27%)	139 (15%)	101 (30%)	14 (23%)	503 (33%)	91 (26%)	19 (28%)	32 (38%)
2010-2012	584 (18%)	95 (11%)	60 (18%)	17 (27%)	325 (21%)	44 (12%)	18 (27%)	25 (29%)
Demographics								
Men	2176 (65%)	542 (61%)	218 (66%)	39 (63%)	1037 (68%)	230 (65%)	49 (73%)	61 (71%)
Age *(men)* Mean(SD) Median(IQR)	71.2 (11.5) 72.2 (15.9)	73.4 (11.9) 75.1 (16.0)	70.9 (11.8) 72.4 (15.6)	73.2 (12.2) 74.9 (13.0)	69.6 (11.6) 70.3 (16.7)	73.3 (9.4) 74.9 (12.1)	72.2 (6.9) 71.6 (9.2)	71.5 (9.4) 73.0 (12.0)
Age*(women)* Mean (SD) Median(IQR)	75.4(11.4) 77.3(14.6)	77.9 (11.4) 80.0 (15.2)	76.2 (9.5) 78.5 (11.9)	76.0 (9.8) 75.3 (11.3)	73.2 (11.8) 74.6 (16.6)	75.6 (10.9) 77.9 (13.4)	75.9 (6.9) 76.3 (11.9)	79.5 (9.1) 82.1 (11.3)
Comorbidity								
Congestive heart failure	892 (27%)	261 (29%)	89 (27%)	20 (32%)	323 (21%)	131 (37%)	31 (46%)	37 (44%)
Cerebrovascular Disease	374 (11%)	131 (15%)	36 (11%)	15 (24%)	125 (8%)	41 (12%)	15 (22%)	11 (13%)
Diabetes with complication	318 (9%)	89 (10%)	40 (12%)	10 (16%)	124 (8%)	38 (11%)	7 (10%)	10 (12%)
Atrial Fibrillation	1020 (31%)	247 (28%)	65 (20%)	47 (76%)	275 (18%)	273 (77%)	48 (72%)	65 (76%)
Other cardiac dysrhythmias	268 (8%)	58 (7%)	14 (4%)	11 (18%)	106 (7%)	59 (17%)	8 (12%)	12 (14%)
Recurrent VTE (>1)	51 (2%)	5 (1%)	6 (2%)	5 (8%)	14 (1%)	16 (5%)	1 (1%)	4 (5%)
Acute renal failure	102 (3%)	36 (4%)	8 (2%)	3 (5%)	38 (3%)	14 (4%)	1 (1%)	2 (2%)
Chronic renal failure	163 (5%)	55 (6%)	18 (5%)	4 (6%)	55 (4%)	21 (6%)	3 (4%)	7 (8%)
Malignant disease	225 (7%)	73 (8%)	29 (9%)	3 (5%)	86 (6%)	30 (8%)	3 (4%)	1 (1%)
Shock	27 (1%)	6 (1%)	2 (1%)	2 (3%)	11 (0.7%)	4 (1%)	1 (1%)	1 (1%)
Pulmonary oedema	77 (2%)	34 (4%)	8 (2%)	3 (5%)	21(1%)	9 (3%)	2 (3%)	0 (0%)
PCI	1437 (43%)	162 (18%)	171 (52%)	7 (11%)	920 (60%)	99 (28%)	34 (51%)	44 (52%)
Pharmacotherapy								
ACEI	1948 (59%)	465 (52%)	211 (64%)	32 (52%)	880 (57%)	245 (69%)	55 (82%)	60 (71%)
Anti-diabetics	468 (14%)	133 (15%)	56 (17%)	15 (24%)	178 (12%)	59 (17%)	13 (19%)	14 (16%)
Beta-blocker	2639 (79%)	611 (69%)	278 (84%)	47 (76%)	1274 (83%)	294 (83%)	59 (88%)	76 (89%)
Loop-diuretics	1439 (43%)	445 (50%)	142 (43%)	38 (61%)	496 (32%)	226 (64%)	43 (64%)	49 (58%)
Spironolactone	395 (12%)	121 (14%)	34 (10%)	6 (10%)	129 (8%)	73 (21%)	19 (28%)	13 (15%)
NSAID	669 (20%)	194 (22%)	63 (19%)	9 (15%)	328 (21%)	55 (16%)	9 (13%)	11 (13%)
PPI	1090 (33%)	300 (34%)	120 (36%)	20 (32%)	490 (32%)	108 (31%)	24 (36%)	28 (33%)
Statins	2497 (75%)	474 (53%)	280 (84%)	26 (42%)	1331 (87%)	255 (72%)	60 (90%)	71 (84%)
First bleeding event								
Cerebral	132 (4%)	44 (5%)	10 (3%)	6 (10%)	54 (3%)	12 (3%)	3 (5%)	3 (4%)
Gastrointestinal	925 (28%)	259 (29%)	88 (27%)	10 (16%)	441 (29%)	92 (26%)	12 (18%)	23 (27%)
Respiratory tract	838 (25%)	144 (16%)	86 (26%)	26 (42%)	416 (27%)	111 (31%)	24 (36%)	31 (36%)
Urogenital	720 (22%)	197 (22%)	78 (23%)	7 (11%)	352 (23%)	62 (18%)	11 (16%)	13 (15%)
Anemia from acute or chronic bleeding	709 (21%)	244 (28%)	70 (21%)	13 (21%)	273 (18%)	77 (22%)	17 (25%)	15 (18%)
Time from MI to bleeding in days *Mean (SD* *Median (IQR)*	145 (104.6) 124 (179.0)	149(108.1) 132 (187.5)	165(99.4) 156(160.5)	158(103.5) 150 (178.0)	139 (104.0) 110 (175.0)	139 (105.3) 115.0 (168.0)	165 (97.5) 154.0 (159.0)	143 (93.3) 112.0 (131.0)

Table 2: Antithrombotic treatments post bleed

Antithrombotic regimen	At the time of bleeding event (baseline) (n=3324)	First antithrombotic regimen within 90 days post bleed* (n=3324)	Antithrombotic regimen day 90 post bleed (n=3324)	Antithrombotic regimen day 180 post bleed (n=3123)
None		736(22.1%)	807(24.3%)	567(18.2%)
Aspirin	888(26.7%)	984(29.6%)	820(24.7%)	1031(33.0%)
Clopidogrel	332(9.9%)	901(27.1%)	485(14.6%)	396(12.7%)
VKAs	62(1.9%)	189(5.7%)	95(2.9%)	96(3.1%)
Aspirin+Clopidogrel (DAPT)	1536(46.2%)	424(12.8%)	870(26.1%)	756(24.2%)
Aspirin+VKA	354(10.7%)	54(1.6%)	129(3.9%)	176(5.6%)
Clopidogrel+VKA	67(2.0%)	22(0.6%)	47(1.4%)	46(1.5%)
Aspirin+Clopidogrel+VKA	85 (2.5%)	14(0.4%)	71(2.1%)	55(1.8%)

***Time from bleeding event to prescription claim (days, mean [SD])**
Aspirin: 42.2 ±26.8 (median 41)
Clopidogrel 31.5 ± 24.3 (median 26)
VKAs 34.4 ± 22.9 (median 32)
Aspirin + Clopidogrel (DAPT) 35.8 ± 26.4 (median 32)
Aspirin + VKA 34.7 ± 26.4 (median 31)
Clopidogrel + VKA 29.2 ± 21.4 (median 26)
Triple therapy 24.2 ± 25.3 (median 13)

Table 3: Assessment of antithrombotic treatment post bleed

	At the time of bleeding event (baseline) (n=3324)	First regimen within 90 days post-bleed (n=3324)	Day 90 post bleed (n=3324)	Day 180 post bleed (n=3123)
Expected treatment	1555(46.8%)	565(17.0%)	1052(31.7%)	1185 (37.9%)
Discontinued treatment	-	736(22.1%)	807(24.3%)	567(18.2%)
Reduced treatment	1374(41.3%)	1914(57.6%)	1301(39.2%)	1089(34.9%)
Intensified treatment	395(11.9%)	109(3.2%)	164(4.9%)	282(9.0%)

Figure

Figure 1: Flowchart of patient selection

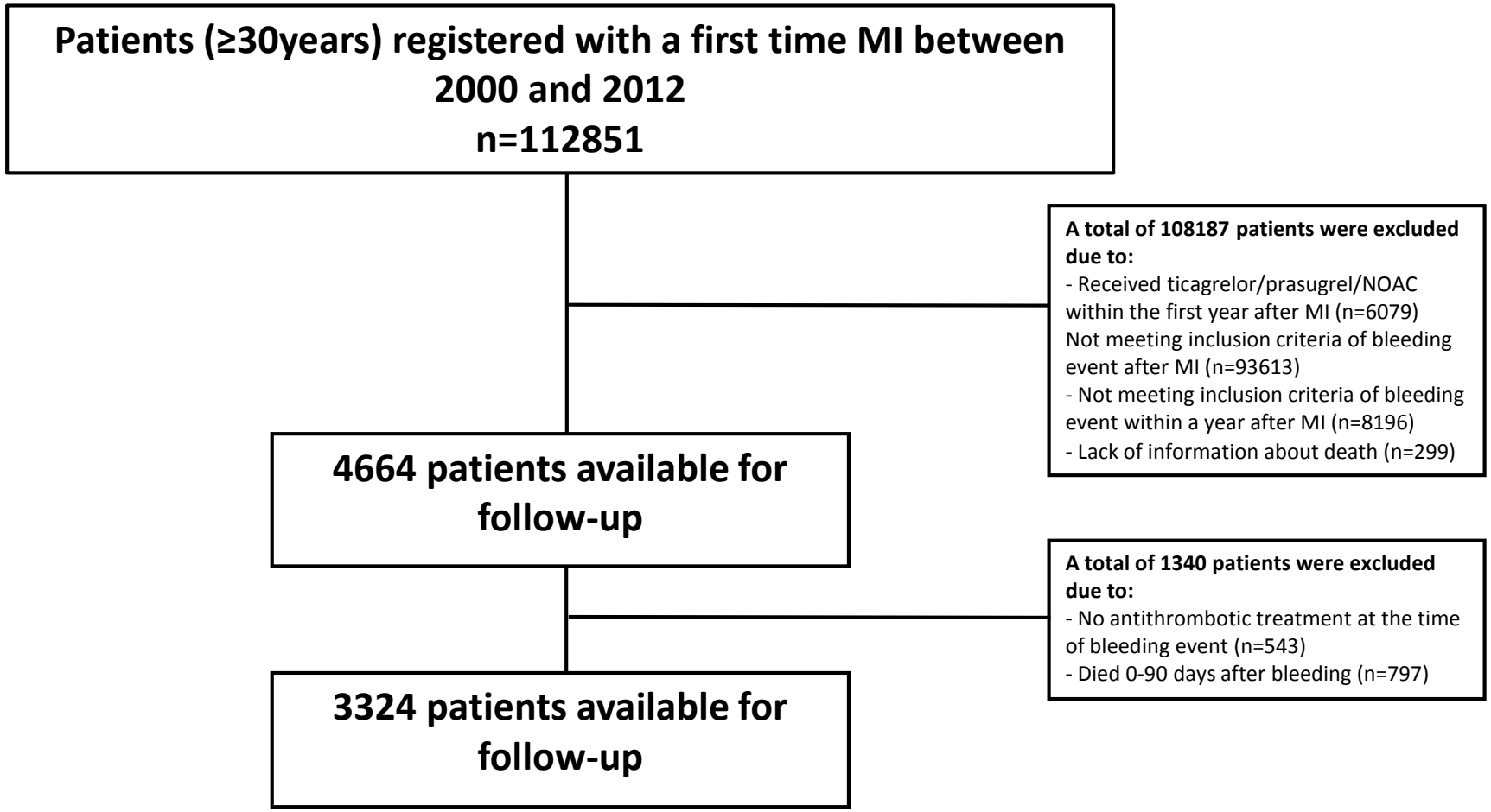
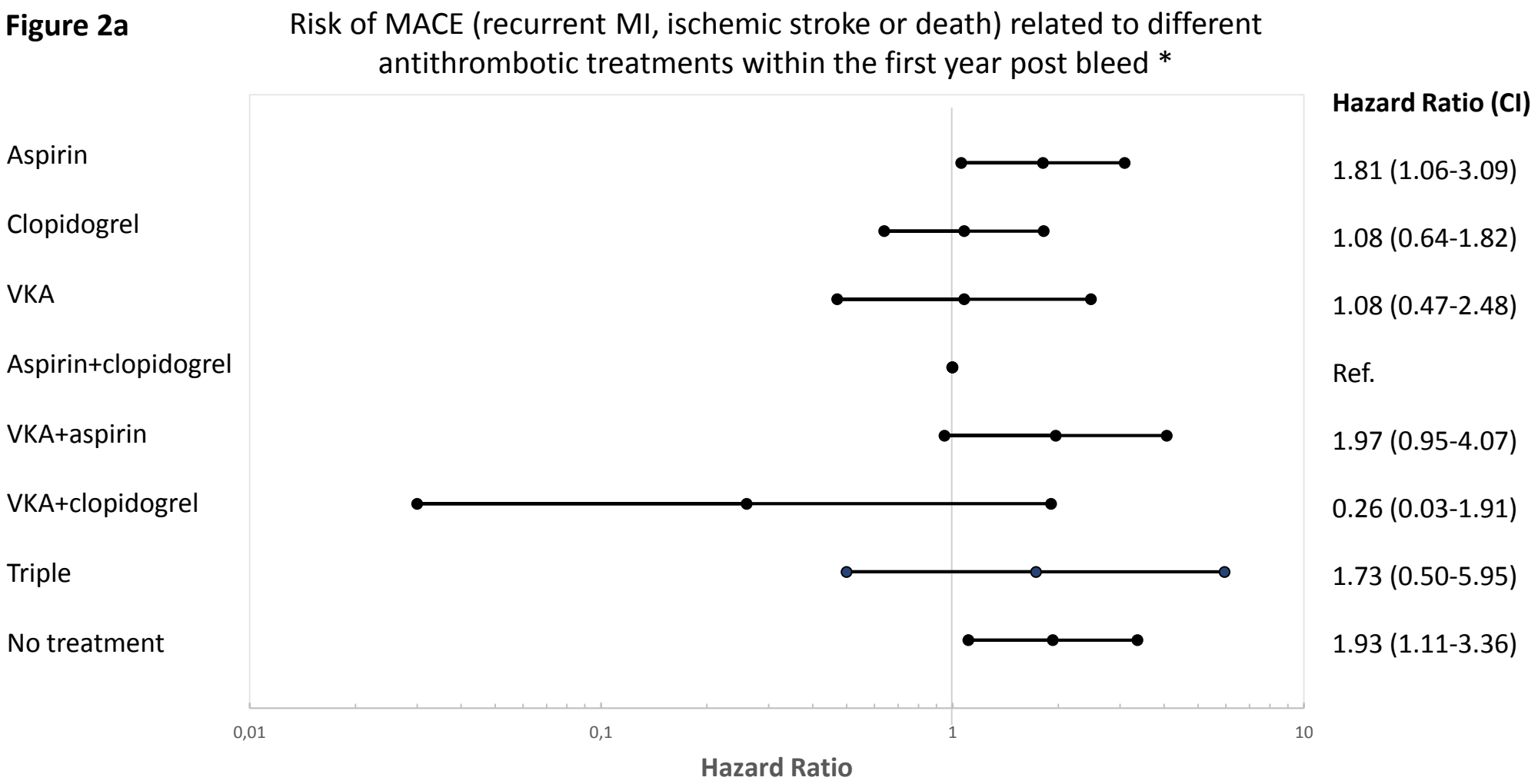
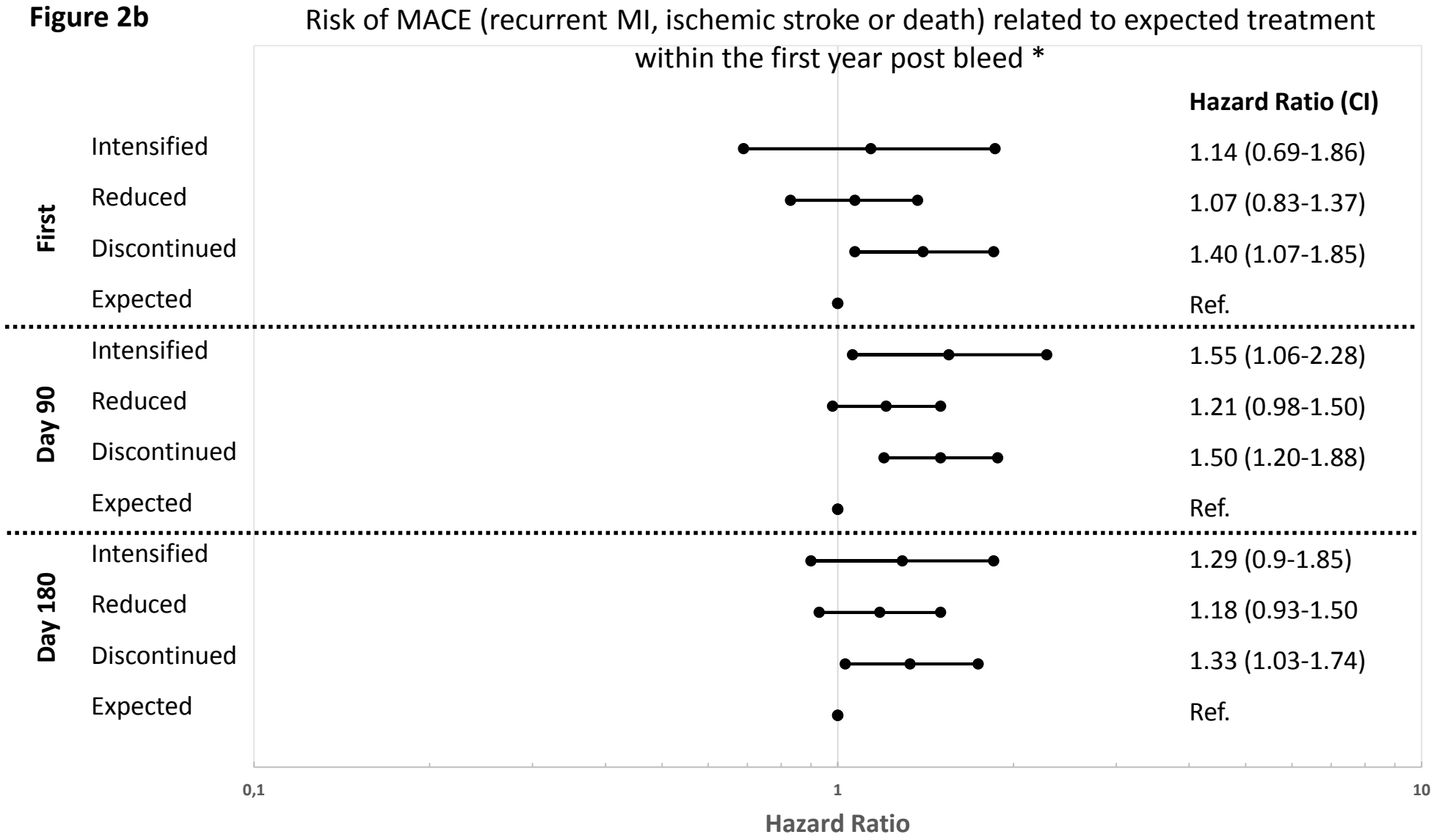


Figure 2a



*The Cox proportional Hazard model had the antitrombotic combinations included as time-dependent variables. The model was adjusted for age groups, sex, comorbidity, concomitant medical therapy and PCI status.

Figure 2b



*The Cox proportional Hazard model was adjusted for age groups, sex, comorbidity, concomitant medical therapy and PCI status.